## *Remarks*

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendments, claims 1, 4, 6-47 and 49-53 are pending in the application, with claims 1 and 49 being the independent claims. Claims 2, 3, and 5 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein.

Claim 1 has been amended to recite "at least one cell type-specific regulatory sequence operably linked to said reporter gene" and "wherein said reporter gene product comprises a secretory leader sequence, and wherein said secreted reporter gene product is not recaptured from said body fluid or cell culture medium." Support for these amendments is found throughout the specification and claims as originally filed, for example, in the specification at page 20, lines 24-31 and in original claims 2 and 5.

Claim 4 has been amended to depend from claim 1 instead of claim 3.

The specification has been amended to recite the priority claims of the captioned application.

These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn. Furthermore, as addressed in more detail below, Applicants respectfully maintain that the special technical feature of the invention is both novel and non-obvious. Accordingly, Applicants respectfully request rejoinder of the claims, at least with respect to the claims of Groups I and II.

***Objection to the Specification***

The specification is objected to for failing to include a paragraph listing the priority information. The specification has been amended herein to list the priority information. Accordingly, Applicants respectfully request that the objection be withdrawn.

***Rejections under 35 U.S.C. § 112, first paragraph***

The rejection of claims 1-9, 11 and 12 under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the written description requirement is respectfully traversed. Claims 2, 3, and 5 have been canceled rendering the rejection moot with respect to these claims.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991). The written description requirement may be satisfied by describing sufficient, relevant, identifying characteristics of the invention, so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. M.P.E.P. § 2163 II.A.3.(a) (citing *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000)). The description need only describe in detail that which is new or not conventional. *Id.* (citing *Hybritech v. Monoclonal Antibodies*, 802 F.2d 1367. (Fed. Cir. 1986)).

Claim 1 is directed to a method for monitoring cell differentiation comprising: (a) culturing cells capable of differentiating into at least one particular cell type wherein said cells contain at least one recombinant nucleic acid molecule comprising a reporter gene encoding a product that is secreted upon cell differentiation and at least one cell type-specific regulatory sequence operably linked to said reporter gene, or maintaining a non-human animal comprising said cells, under conditions allowing differentiation of said cells; and (b) determining the amount or activity of the reporter gene product within a body fluid of said transgenic non-human animal or the cell culture medium of said cells, wherein said reporter gene product comprises a secretory leader sequence, and wherein said secreted reporter gene product is not recaptured from said body fluid or cell culture medium. Claims 4, 6-9, 11 and 12 depend from claim 1 and incorporate all of its elements.

As an initial matter, Applicants respectfully submit that an aspect of the invention is the recognition that *secreted* reporter genes can be used successfully to monitor cell differentiation. Prior to this invention, *intracellular* reporter genes were the exclusive

art-accepted reporter genes for monitoring cell differentiation. Once this invention was made, *i.e.,* once it was recognized that secreted reporter genes can be successfully used to monitor cell differentiation, Applicants were in full possession of the claimed method because the reporter genes, tissue specific regulatory elements, cell lines and tissue culture methods used to practice the claimed method were known in the art and are sufficiently described in the captioned specification.

Applicants further submit that claim 1 has been amended to recite, *inter alia*, (1) that the secreted reporter gene is operably linked to a cell type-specific regulatory sequence, and (2) that the reporter gene product comprises a secretory leader sequence. These amendments render moot any rejection for an alleged failure to provide adequate written description of a reporter gene that is not operably linked to a regulatory sequence, or of a secreted reporter gene product that does not comprise a secretory leader sequence. Office Action ("OA"), p. 3, ¶6 and p. 4, ¶2.

In support of the rejection, the OA at page 3, paragraph 6 asserts that the specification

> only teaches the expression of a gene encoding a secretory product SEAP under the control of a promoter of mouse alpha-myosin gene and does not tech [sic] any other reporter gene under the control of any other promoter or regulatory sequence . . . . [and] only teaches cells which form embryoid bodies and does not teach any other cell aggregates or tissue aggregates.

Applicants respectfully submit that, contrary to the Office's assertion, the specification describes a sufficient number of secreted reporter genes, regulatory elements and differentiation capable cell lines by their complete structure, or by relevant identifying characteristics, to provide adequate written description for the entire scope of the method of claim 1.

The specification adequately describes the genus of secreted reporter genes that may be used to practice the claimed method by providing the relevant identifying characteristics that the secreted reporter gene product (1) is not recaptured from the cell culture supernatant or body fluid and (2) can be quantified by measuring its activity or concentration. Captioned specification, p. 20, ll. 24-31. The specification further adequately describes the SEAP, alpha-amylase and invertase secreted reporter genes, two

of which are recited in claim 9, because the complete structure of these reporters was known in the art at the time the application was filed. *Id.*, p. 21 ll. 19-29 and p. 22, ll. 1-2; *Falkner v. Inglis,* 448 F.3d 1357 (Fed. Cir. 2006), recitation of a known structure is not required to satisfy written description requirement. Accordingly, Applicants respectfully submit that the specification provides adequate written description for the full scope of secreted reporter genes recited in claims 1 and 9.

The specification also describes a large number of tissue specific regulatory sequence elements that may be used to practice the claimed method. *See, e.g.,* captioned specification, pp. 18-19, bridging paragraph, p. 21, ll. 6-17 and p. 39, ll. 23-31. The described regulatory sequence elements include, for example, the αMHC, MLC2V, VE-cadherin, Tie-2, Flk-1, Flt-1, GFAP, alpha-1-tubulin and collagen 2 promoter or enhancer, as recited in rejected claim 8. *Id.*, p. 18, ll. 19-20. Because the complete structure, as well as the tissue specificity of all of the described regulatory elements was known in the art at the time the application was filed, the specification provides adequate written description of the full scope of regulatory sequence elements recited in claims 1, 6 and 8.

The specification additionally adequately describes a number of cell lines that may be used to practice the claimed method. *See, e.g.,* captioned specification, p. 13, ll. 24-31, pp. 14-15. The cell lines described include already differentiated precursor cells that may be differentiated into a particular mature cell type, as well as pluripotent stem cell populations, as recited in claim 4. The specification further adequately describes tissue culture systems that were designed to guide cellular differentiation towards a particular tissue or cell type, as recited in rejected claim 7. *Id.,* p. 16-17, bridging paragraph. The specification also adequately describes that ES cells may be differentiated under conditions that lead to the formation of cell aggregates or tissue-like aggregates, including embryoid bodies, as recited in claims 11 and 12. *See, e.g.,* captioned specification pp. 23-24. The specification further adequately describes alternative differentiation systems that use spinner flasks that eontinuously stir the differentiating cells. *Id.*, pp. 24-25, bridging paragraph. Accordingly, the disclosures within the specification related to the cells capable of differentiating, as well as to the conditions allowing differentiation of the cells, in combination with the teachings of the

art, provides adequate written description for the entire scope of claims 1, 4, 7, 11 and 12.

At least for the above reasons, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the written description requirement be reconsidered and withdrawn.

The rejection of claims 1-9, 11 and 12 under 35 U.S.C. § 112, first paragraph for alleged lack of enablement is respectfully traversed. Claims 2, 3 and 5 have been canceled rendering the rejection moot with respect to these claims.

The Office acknowledges that the specification is "enabled for a method of monitoring differentiation of stem cell into specific cell lineage by measuring the amount of secreted activity of a reporter gene product by the differentiated cell wherein said gene expressed in the differentiating cell under the control of a operatively linked tissue specific regulator/promoter specific to said differentiating cells." OA, p. 5, ¶1 (emphasis added). The OA further asserts that the specification is "not enabled for reporter gene encoding a product without an operatively linked signal sequence or leader sequence." *Id.*

Solely to expedite prosecution, claim 1 has been amended to recite that the at least one recombinant nucleic acid molecule comprising a reporter gene encoding a product that is secreted upon cell differentiation also comprises at least one cell type-specific regulatory sequence operably linked to said reporter gene. Claim 1 has further been amended to recite that the reporter gene product comprises a secretory leader sequence. Applicants respectfully submit that by the Office's own acknowledgement, referenced above, the specification is enabling for amended claim 1.

Claims 4, 6-9, 11, and 12 depend from claim 1 and incorporate all of its elements. Because the specification is enabling for claim 1, Applicants respectfully submit that the specification is also enabling for claims 4, 6-9, 11, and 12.

At least for the above reasons, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph for alleged lack of enablement be reconsidered and withdrawn.

***Rejections under 35 U.S.C. § 102***

The rejection of claims 1-8 and 11 under 35 U.S.C. § 102(b) for allegedly being anticipated by Goldspink *et al.*, U.S. Publication No. 2003/0008836 ("Goldspink") is respectfully traversed. Claims 2, 3, and 5 have been canceled rendering the rejection moot with respect to these claims.

Claim 1 is directed to a method of for monitoring cell differentiation comprising, *inter alia,* determining the amount or activity of a secreted reporter gene product within a body fluid or cell culture medium wherein the secreted reporter gene product is not recaptured from the body fluid or cell culture medium. Claims 4, 6-8, and 11 depend from claim 1 and incorporate all of its elements.

Applicants respectfully submit that Goldspink does not anticipate the rejected claims because Goldspink does not recite each and every element as set forth in claims 1, 4, 6-8 and 11. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Goldspink allegedly discloses "the transfecting [of] recombinant nucleic acid molecules encoding a human alpha-gal reporter gene under the control of promoter comprising MLC1/3 enhancer to undifferentiated myoblasts wherein the reporter gene was expressed and secreted from differentiated muscle cell in vitro culture." OA, p. 6, ¶5 (citing Goldspink, paragraphs 52-59) (emphasis added). Goldspink, however, does not disclose, *inter alia*, a secreted reporter gene product that is not recaptured from the culture medium as recited in the rejected claims because secreted human alpha-gal is recaptured from the tissue culture medium. *See, e.g.*, Goldspink, ¶¶3 and 57, and Figure 4.

At least for the above reasons, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

***Rejections under 35 U.S.C. § 103***

The rejection of claims 1-9, 11, and 12 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Wobus *et al., J. Mol. Cell. Cardiol.*, 29:1525-1539 (1997) ("Wobus") in view of Benkel *et al.*, PCT Publication No. WO 98/49320 ("Benkel") is

respectfully traversed. Claims 2, 3, and 5 have been canceled rendering the rejection moot with respect to these claims.

In *KSR International v. Teleflex, Inc.*, 127 S.Ct. 1727 (2007), the Supreme Court clarified the requirements for a proper obviousness analysis under 35 U.S.C. § 103(a). The Court noted that the analysis supporting a rejection under 35 U.S.C. § 103(a) should be made *explicit*, and that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements in the way the claimed new invention does." *Id.* at 1741. The Court also stated that "[r]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *Id.*, quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

However, "[i]f [the] proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." M.P.E.P. § 2143.01, Section V (citing *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984).

In addition, "[i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious." M.P.E.P. § 2143.01, Section VI (citing *in re Ratti*, 270 F.2d 810 (CCPA 1959)).

Applicants respectfully submit that under *In re Gordon*, Wobus, in view of Benkel, is not sufficient to support a *prima facie* case of obviousness because the proposed modification renders Wobus' monitoring method unsatisfactory for its intended purpose. Wobus discloses the use of an *intracellular* reporter gene, *i.e.*, the MLC-2v promoter expressed beta-galactosidase, to monitor cardiocyte differentiation and specialization into ventricle-like cardiomyocytes. Wobus, Abstract. An intracellular reporter, such as beta-galactosidase, accumulates within the cell that expresses it. Because of this accumulation, an intracellular reporter conveys spatial information about gene expression. For example, Wobus used histochemical staining techniques to determine which cells within an embryoid body outgrowth expressed the beta-

galactosidase reporter. Wobus, p. 1527, right column, ¶3. Wobus relied on this spatial information conveyed by the intracellular reporter to monitor cardiocyte differentiation. For example, Wobus disclosed the percent (%) of embryoid body outgrowths that expressed the intracellular reporter, as well as the percent (%) area per embryoid body outgrowths that expressed the intracellular reporter under different culture conditions. Wobus, Figure 1 (b)-(e).

In contrast, present claim 1 is directed to a method for monitoring cell differentiation comprising, *inter alia*, culturing cells capable of differentiating into at least one particular cell type wherein said cells contain at least one recombinant nucleic acid molecule comprising a reporter gene encoding a product that is *secreted* upon cell differentiation under conditions allowing differentiation of said cells; and determining the amount or activity of the reporter gene product within the cell culture medium of said cells. A secreted reporter, *e.g.,* a reporter disclosed by Benkel, is by definition separated from the cell that expresses it, and is detected by analyzing a sample of the extracellular medium. Benkel, p. 1, ll. 9-10 and 14-16. Because a secreted reporter is separated from the cell that expresses it, the secreted reporter cannot convey spatial information about reporter expression within a heterogeneous system, such as a culture comprising a population of embryoid body outgrowths.

Applicants respectfully submit that the proposed modification to Wobus would render Wobus unsatisfactory for its original intended purpose. By exchanging the *intracellular* reporter of Wobus, *i.e.*, beta-galactosidase, for a *secreted* reporter, *e.g.*, SEAP or alpha-amylase, the ability of collecting spatial information about reporter expression within the differentiating structures will be lost. Because Wobus relied, at least in part, on spatial information to monitor cardiocyte differentiation, the proposed modification would render Wobus' monitoring method unsatisfactory for its intended purpose.

Applicants additionally submit that Wobus is not alone in choosing an intracellular reporter, over a secreted reporter, to monitor cell differentiation. Bremer (Bremer *et al.*, *Toxicology In Vitro* 13(4-5):619-23 (a copy of which is submitted with the Supplemental IDS filed concurrently with this paper)) discloses the establishment of

an *in vitro* reporter gene assay for developmental cardiac toxicity. Bremer utilizes a GFP based intracellular reporter in his assay. Bremer, Section 3.1. Like Wobus, Bremer also collected spatial information about reporter expression, that is Bremer analyzed GFP expression in individual developing cells using a flow cytometer. Bremer, Figure 1. Flow cytometry allowed Bremer to focus on the cardiac cells within the larger heterogeneous population of differentiating ES cells. Bremer, p. 218, right column, ¶3.

Furthermore, Applicants respectfully submit that, under *In re Ratti*, Wobus in view of Benkel is not sufficient to render the claims *prima facie* obvious because the proposed modification or combination of the cited art changes Wobus' principle of operation. M.P.E.P. at § 2143.01, Section VI (citing *In re Ratti*, 270 F.2d 810 (CCPA 1959)). The proposed modification to Wobus, *i.e.*, the exchange of an *intracellular* reporter for a *secreted* reporter, would change the principle of operation of Wobus' monitoring method because Wobus' monitoring method relies, at least in part, on the intracellular reporter's ability to convey spatial information about the reporter expression within a developing embryoid body outgrowth. Wobus, Figure 1 (b)-(e).

For at least these reasons, Applicants respectfully submit that the Office has not established the *prima facie* obviousness of independent claim 1. Because claims 4, 6-9, 11 and 12 depend from, and incorporate every element of claim 1, these claims are likewise not obvious over Wobus, in view of Benkel.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

***Additional Matters - Double Patenting Warning***

Applicants were advised that should claim 1 be found allowable, claim 3 would be objected to under 37 C.F.R. § 1.75 as being a substantial duplicate thereof. OA, p. 8, ¶2. Solely to expedite prosecution, Applicants have canceled claim 3.

## *Conclusion*

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of these Amendments and Reply is respectfully requested.

Respectfully submitted,

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